Hemostasis

by

Mohie-Aldien Elsayed
Hemostasis

Hemostasis is defined as the process that maintains the flowing blood in a fluid state and confined to the circulatory system.

Coagulation prevents excess blood loss or hemorrhage. Excessive clotting, thrombogenesis, would lead to arterial blockage.

*The normal hemostatic mechanism consists of a balance between hemorrhage & thrombosis which achieved through the interaction of four component parts; *the blood vessels, *platelets, *the coagulation and anticoagulant factors, *the fibrinolytic factors
Hemostasis: Vasoconstriction & Plug Formation

- A series of reactions designed for stoppage of bleeding
- During hemostasis, three phases occur in rapid sequence:
  * Vasoconstriction
  * Platelet activation (Multiple factors, Positive feedback)
  * Aggregation
  * Loose plug
  - Coagulation (blood clotting)
Hemostasis: Vasoconstriction & Plug Formation

Figure 16-12: Platelet plug formation

1. Exposed collagen binds and activates platelets.
2. Release of platelet factors.
3. Attracts more platelets.
4. Aggregate into platelet plug.
Hemostasis
The Vascular and Platelet Phases of Hemostasis

**Vascular Phase**
- Blood vessel injury
- Vascular spasm

**Platelet Phase**
- Release of chemicals (ADP, thromboxane A$_2$, Ca$^{2+}$, platelet factors)
- Platelet adhesion
- Platelet aggregation
- Contracted smooth muscle cells
- Cut edge of vessel wall

**Diagram Elements**
- Vessel lumen
- Endothelium
- Basal lamina
- Vessel wall
- Concentric smooth muscle
- Interstitial fluid
- Blood
Injury of vessels wall leads to contact between blood and subendothelial cells

Tissue factor (TF) is exposed and binds to FVIIa or FVII which is subsequently converted to FVIIa

The complex between TF and FVIIa activates FIX and FX

FXa binds to FVα on the cell surface

1. Initiation phase
The FXa/FVa complex converts small amounts of prothrombin into thrombin.

The small amount of thrombin generated activates FVIII, FV, FXI, and platelets locally. FXIa converts FIX to FIXa.

Activated platelets bind FVa, FVIIIa and FIXa.
The FVIIIa/FIXa complex activates FX on the surfaces of activated platelets.

FXa in association with FVa converts large amounts of prothrombin into thrombin creating a “thrombin burst”.

The “thrombin burst” leads to the formation of a stable fibrin clot.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-II</td>
<td>Angiotensin-II</td>
</tr>
<tr>
<td>bFGF</td>
<td>basic Fibroblast Growth Factor</td>
</tr>
<tr>
<td>ET-1</td>
<td>Endothelin-1</td>
</tr>
<tr>
<td>HeSu</td>
<td>Heparansulphates</td>
</tr>
<tr>
<td>ICAM-1</td>
<td>InterCellular Adhesion Molecule-1</td>
</tr>
<tr>
<td>IL-1 (-8)</td>
<td>Interleukin-1 (-8)</td>
</tr>
<tr>
<td>MCP-1</td>
<td>Monocyte Chemoattractant Factor-1</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric Oxide</td>
</tr>
<tr>
<td>PAI-1</td>
<td>Plasminogen Activator Inhibitor-1</td>
</tr>
<tr>
<td>PDGF</td>
<td>Platelet Derived Growth Factor</td>
</tr>
<tr>
<td>PECAM-1</td>
<td>Platelet-endothelium Cell Adhesion Molecule-1</td>
</tr>
<tr>
<td>PGH₂</td>
<td>Prostaglandin H2</td>
</tr>
<tr>
<td>PGJ₂</td>
<td>Prostaclicin</td>
</tr>
<tr>
<td>Sel-E (−P)</td>
<td>Selectin-E (−P)</td>
</tr>
<tr>
<td>TGFα (β)</td>
<td>Transforming Growth Factor α (β)</td>
</tr>
<tr>
<td>T-Spond</td>
<td>Thrombospondin</td>
</tr>
<tr>
<td>t-IPA</td>
<td>tissue-type Plasminogen Activator</td>
</tr>
<tr>
<td>TxA₂</td>
<td>Thromboxan A2</td>
</tr>
<tr>
<td>VWF</td>
<td>von Willebrand Factor</td>
</tr>
<tr>
<td>5-HT</td>
<td>Serotonin</td>
</tr>
</tbody>
</table>
The Coagulation Phase of Hemostasis

Factors released by platelets and endothelial cells interact with clotting factors to form a clot

- Extrinsic pathway
- Intrinsic pathway
- Common pathway

- Suspended fibrinogen is converted to large insoluble fibrin fibers

(b) A blood clot
Haemostasis & Thrombosis
- Adhesion
- Activation
- Spreading
- Secretion
- Aggregation
- Procoagulant activity
- Clot retraction
- Tissue Repair

Maintenance/Regulation of Vascular Tone
- Uptake of serotonin when resting
- Release of serotonin, thromboxane, prostaglandins upon activation

Platelet Functions

Inflammation
- Atherosclerosis
- Allergic Asthma
- Renal Disease
- Chemotaxis
- Platelet-Leukocyte interactions

Host Defence
- Phagocytosis/Internalisation of Viruses and Bacteria
- Killing of Bacteria
- Release of Platelet microbicidal proteins
- Superoxide production

Tumour Biology
- Tumour Growth
- Tumour killing
- Tumour Metastasis
Blood Platelets
formed from the cytoplasm of bone marrow megakaryocytes.

- Normal platelet count lies between 150-400 x 10^9/L
- Disc-shaped, anucleated cells with complex internal structure

\[\text{dense granules (because of their appearance on EM) contain: ADP, ATP & 5HT and serotonin.}\]

\[\alpha\text{-granules (fibrinogen, von-Willebrand F., factors V & VIII, fibrinectin, B-thromboglobulin, Heparin antagonist (PF4), thrombospondin)}; \text{ platelet-derived growth factor (PDGF).}\]
The Coagulation Phase of Hemostasis

(a) The coagulation phase
Clot retraction

• Final phase of healing
• Platelets contract and pull the edges of the vessel together
Fibrinolysis

• Clot gradually dissolves through action of plasmin
  – Activated form of plasminogen
• Clotting can be prevented through the use of drugs that depress the clotting response or dissolve existing clots
  – Anticoagulants include heparin, coumadin, aspirin, dicumarol, t-PA, streptokinase, and urokinase
Administering excess tPA can deplete anti-plasmin levels leading to a systemic lysis state due to the unrestrained protease action of plasmin.

Aminocaproic acid acts as a fibrinolysis inhibitor by blocking these lys-rich sites.
Hemostasis: Coagulation & Clot Stabilization

- Prothrombin
- Ca++
- Fibrinogen
- Fibrin
- Polymerization
B. Activation of clotting

C. Inhibition of clotting by removal of Ca$^{2+}$
Vit. K<sub>1</sub> (Phytomenadione)

Vit. K<sub>2</sub> (Menadione)

Vit. K<sub>3</sub>

Duration of action/days

- Phenprocoumon
- Warfarin
- Acenocoumarol

Carboxylation of glutamine residues

Vit. K derivatives

4-Hydroxy-Coumarin derivatives
Presystemic inactivation of platelet cyclooxygenase by acetylsalicylic acid
Coagulation

• A set of reactions in which blood is transformed from a liquid to a gel
• Coagulation follows intrinsic and extrinsic pathways
• The final three steps of this series of reactions are:
  – Prothrombin activator is formed
  – Prothrombin is converted into thrombin
  – Thrombin catalyzes the joining of fibrinogen into a fibrin mesh
# Summary of Formed Elements

## Table 17.2: Summary of Formed Elements of the Blood

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Illustration</th>
<th>Description*</th>
<th>Cells/mm³ (μl) of Blood</th>
<th>Duration of Development (D) and Life Span (LS)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erythrocytes</strong> (red blood cells, RBCs)</td>
<td><img src="image1.png" alt="Illustration" /></td>
<td>Biconcave, anucleate disc; salmon-colored; diameter 7–8 μm</td>
<td>4–6 million</td>
<td>D: 5–7 days LS: 100–120 days</td>
<td>Transport oxygen and carbon dioxide</td>
</tr>
<tr>
<td><strong>Leukocytes</strong> (white blood cells, WBCs)</td>
<td><img src="image2.png" alt="Illustration" /></td>
<td>Spherical, nucleated cells</td>
<td>4800–10,800</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Neutrophil</td>
<td><img src="image3.png" alt="Illustration" /></td>
<td>Nucleus multilobed; inconspicuous cytoplasmic granules; diameter 10–12 μm</td>
<td>3000–7000</td>
<td>D: 6–9 days LS: 6 hours to a few days</td>
<td>Phagocytize bacteria</td>
</tr>
<tr>
<td>- Eosinophil</td>
<td><img src="image4.png" alt="Illustration" /></td>
<td>Nucleus bilobed; red cytoplasmic granules; diameter 10–14 μm</td>
<td>100–400</td>
<td>D: 6–9 days LS: 8–12 days</td>
<td>Kill parasitic worms; destroy antigen-antibody complexes; inactivate some inflammatory chemicals of allergy</td>
</tr>
</tbody>
</table>

*Appearance when stained with Wright’s stain.

Table 17.2
### Summary of Formed Elements of the Blood (continued)

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Illustration</th>
<th>Description*</th>
<th>Cells/mm³ (μl) of Blood</th>
<th>Duration of Development (D) and Life Span (LS)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basophil</td>
<td><img src="image" alt="Basophil Illustration" /></td>
<td>Nucleus lobed; large blue-purple cytoplasmic granules; diameter 8–10 μm</td>
<td>20–50</td>
<td>D: 3–7 days LS: ? (a few hours to a few days)</td>
<td>Release histamine and other mediators of inflammation; contain heparin, an anticoagulant</td>
</tr>
<tr>
<td>Agranulocytes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocyte</td>
<td><img src="image" alt="Lymphocyte Illustration" /></td>
<td>Nucleus spherical or indented; pale blue cytoplasm; diameter 5–17 μm</td>
<td>1500–3000</td>
<td>D: days to weeks LS: hours to years</td>
<td>Mount immune response by direct cell attack or via antibodies</td>
</tr>
<tr>
<td>Monocyte</td>
<td><img src="image" alt="Monocyte Illustration" /></td>
<td>Nucleus U or kidney shaped; gray-blue cytoplasm; diameter 14–24 μm</td>
<td>100–700</td>
<td>D: 2–3 days LS: months</td>
<td>Phagocytosis; develop into macrophages in tissues</td>
</tr>
<tr>
<td>Platelets</td>
<td><img src="image" alt="Platelet Illustration" /></td>
<td>Discoid cytoplasmic fragments containing granules; stain deep purple; diameter 2–4 μm</td>
<td>150,000–400,000</td>
<td>D: 4–5 days LS: 5–10 days</td>
<td>Seal small tears in blood vessels; instrumental in blood clotting</td>
</tr>
</tbody>
</table>

*Appearance when stained with Wright’s stain.

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Table 17.2
Genesis of Platelets

• The stem cell for platelets is the hemocytoblast

• The sequential developmental pathway is hemocytoblast, megakaryoblast, promegakaryocyte, megakaryocyte, and platelets

Figure 17.12
(Endothelium rupture → collagen exposure)
Blood Components
Overview of Hemostasis: Clot Formation & Vessel Repair